SCIENTIFIC ABSTRACT

The purpose of this study is to determine whether CD34+ cells from umbilical cord blood or bone marrow of ADA-deficient infants/children can be transduced by retroviral-mediated transfer of a normal human ADA cDNA, can be safely infused intravenously, and will engraft and produce mature peripheral blood leukocytes containing and expressing the ADA cDNA. Potentially, the development of T lymphocytes expressing ADA could restore functional immunity in the absence of exogenous PEG-ADA enzyme replacement therapy. A secondary purpose of the study is to compare the activity of two retroviral vectors, GCsap-M-ADA and MND-ADA, for their relative abilities to contribute to immune reconstitution.

The study is open to infants diagnosed *in utero* / or children with ADA-deficiency and SCID who are not candidates for HLA-identical sibling donor bone marrow transplantation. Umbilical cord blood/bone marrow will be collected at parturition/during childhood and CD34+ cells will be isolated. The CD34+ cells will be divided into two equal portions and transduced either by the GCsap-M-ADA or the MND-ADA retroviral vectors. Transduction will be augmented with recombinant MGDF (a thrombopoietin), Stem Cell Factor and flt-3 ligand, using recombinant fibronectin CH-296 as a support matrix. After transduction, the cells will be re-mixed and infused intravenously into their donors without prior cytoreductive therapy. Infants will be started, and children maintained, on enzyme replacement with PEG-ADA at standard dosages (45-60 U/kg/week).

Serial samples of peripheral blood will be analyzed for the frequency of cells containing the inserted ADA vectors. Expression of the ADA cDNA from the vectors will be analyzed by RT-PCR and enzyme assay. If persistent production of cells containing and expressing the ADA gene is achieved, the dosages of PEG-ADA may be reduced or withdrawn to observe the effects on the levels and function of transduced T lymphocytes.

In all, these studies will seek to determine the safety and efficacy of ADA gene transfer into autologous umbilical cord blood/bone marrow CD34+ cells to provide functional immunity and allow withdrawal of exogenous enzyme replacement therapy.